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DATE: Friday, March 18, 2005

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,USOC; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L8	($1IAPP or islet beta amyloid?) same (d-amino acid? or D$amino or D-peptide or D$epptide or D-form?)	6
☐	L7	($1IAPP or islet beta amyloid?) and (d-amino acid? or D$amino or D-peptide or D$epptide or D-form?)	76
☐	L6	(IAPP or islet beta amyloid?) smame (d-amino acid? or D$amino or D-peptide or D$epptide or D-form?)	0
☐	L5	6303567.pn.	1
☐	L4	amyloid same $peptide? same (D-form? or D-amino acid? or D4isomer?)	21
☐	L3	amyloid and (D-form? or D-amino acid? or D4isomer?)	358
☐	L2	findels and amyloid and (D-form? or D-amino acid? or D4isomer?)	0
☐	L1	findels and amyloid same (D-form? or D-amino acid? or D4isomer?)	0

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Search Results - Record(s) 1 through 6 of 6 returned.

1. Document ID: US 20040248876 A1

L8: Entry 1 of 6 File: PGPB Dec 9, 2004

DOCUMENT-IDENTIFIER: US 20040248876 A1
TITLE: Methods and compounds for inhibiting amyloid deposits

Detail Description Paragraph:
[0064] Certain compounds (or their salts, as noted) as disclosed herein, i.e., 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; 2-amino-5-phosphovaleric acid; 4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrah- ydropyridine; cyclohexylsulfamic acid; O-phospho-L-serine; hexafluoroglutaric acid; 8-methoxy-5-quinolinesulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesu- lfonic acid, and 1,2,3,4-tetrahydroisoquinoline, were found, using this assay, to inhibit or prevent IAPP-associated fibril assembly.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

2. Document ID: US 20040198832 A1

L8: Entry 2 of 6 File: PGPB Oct 7, 2004

DOCUMENT-IDENTIFIER: US 20040198832 A1
TITLE: Compositions and methods for treating amyloidosis

Detail Description Paragraph:
[0135] Certain compounds as disclosed herein, i.e., 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tet- rahydropyridine; cyclohexylsulfamic acid; .beta.-phospho-L-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and 1,2,3,4-tetrahydroisoquinoline, were found to inhibit or prevent IAPP-associated fibril assembly.

Detail Description Table CWU:
6 Compound Activity T.sub.0 24 h 48 h Control IAPP -- Random .beta. (-2) .beta. (-1.5) 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid Active Random Random .beta. (-1.7) (LVX) DL-2-amino-5-phosphovaleric acid (LVIII) Active Random Random .beta. (-3.5) 1,2,3,4-tetrahydroisoqu- inoline(LVIX) Active Random .beta. (-1.5) .beta. (-1.3) cyclohexylsulfamic acid(LVXI) Active Random .beta. (-1.1) .beta. (-0.8) O-phospho-L-serine (LVXII) Active Random Random .beta. (-2.0) 8-methoxyquinoline-5-sulfonic acid(LVXIV) Active Random .beta. (-1.3) .beta. (-0.8) 4-Phenyl-1-(3'-

sulfopropyl)-1,2,3,6-tetrahydropyridi- ne, Active Random Random .beta. (-1.8) sodium salt (LVXV) 3-amino-2-hydroxy-1-propanesulfonic acid (LVXVI) Active -- -- -- 3-dimethylamino-1-propanesulfonic acid (LVXVII) Active Random .beta. (-1.7) .beta. (-1.5)

☐ 3. Document ID: US 20020094335 A1

L8: Entry 3 of 6 File: PGPB Jul 18, 2002

DOCUMENT-IDENTIFIER: US 20020094335 A1
TITLE: Vaccine for the prevention and treatment of alzheimer's and amyloid related diseases

Detail Description Paragraph:
[0081] Specifically, the A.beta.(16-21) site is known to play an important role in initiating the harmful process of A.beta. peptide amyloidogenesis. It is also known that when these peptides are made from D-amino acids, they retain their ability to interact with the natural all-L-homologous sequence, thereby preventing amyloidogenesis. Other amyloid proteins which may be used in the present invention include, without limitation, the beta sheet region of IAPP (24-29, all-D), .beta.2-microglobulin, amyloid A protein, and prion-related proteins.

☐ 4. Document ID: US 6562836 B1

L8: Entry 4 of 6 File: USPT May 13, 2003

DOCUMENT-IDENTIFIER: US 6562836 B1
** See image for Certificate of Correction **
TITLE: Methods and compounds for inhibiting amyloid deposits

Detailed Description Text (44):
Certain compounds (or their salts, as noted) as disclosed herein, i.e., 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; 2-amino-5-phosphovaleric acid; 4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; O-phospho-L-serine; hexafluoroglutaric acid; 8-methoxy-5-quinolinesulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and 1,2,3,4-tetrahydroisoquinoline, were found, using this assay, to inhibit or prevent IAPP-associated fibril assembly.

CLAIMS:

104. The method of claim 1, wherein said IAPP-inhibiting compound is selected from the group consisting of the compounds 3-[2-(6-dimethylamino-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, and pharmaceutically acceptable esters, acids, and salts thereof.

5. Document ID: US 3114724 A

L8: Entry 5 of 6 File: USOC Dec 17, 1963

DOCUMENT-IDENTIFIER: US 3114724 A
TITLE: Low temperature expansion of liquid organic polysulfide polymer with metal hydrides, borohydrides or aluminum hydrides

OCR Scanned Text (2):
3,114,724 3 p roducing @ubbery vulcanizates from liqiiid polysulfide p olymers, the cur!ing a.@entvvill be added just piior to us-@ a nd @thus perform the double funetion of C-uring the p olyme,r a@nd decomposingthe blowing ,igent, resulting in th e foimation of ian expand@d and cured produot. @In 5 s o,n-te cases it is convenient to a-Ilow the polysulfide com- p osition coi@taining the fnetalliydride or borohydride and ,t, be ctiratives to st-and at room or ambient @Lemperattixe (e ..,., around 10-35' C.) overnight or for several days. D uring this period @"p@ans@ion and cure slo-wly take place. 1 0 ,a nd a stable collular product is produced. A p,articularly v aluable iapp-lication of this tcohnique will b.- found in fo amed-in-p,l,ace caulking and gasketing. T he qu@antity of metal hydride or @borohydride used may v ary over v,,ide iliniits depending @tipon the degree of ex- 1 5 p ansion de,sired. Generally, the quantity of the - bloiwing a, ,@elit used - will be between 0.1% and 10% of the poly- s ujfide rubber used. I-lowever, greater or less than the q uantities indicated can be u;sed; @and it is not intended to di n-ii,t,the invention -to the quantities of the blowing agent 2 0 ,d esoribed. Likewise th-@ amount of curing (oxidizing) a, -ent may be -adjus@ted over a considerable range to; pro- vi de piroper icure and to effectively de,compose the bilow- in g @agent. In any case the amount of oxidizi 'ng agent ei 'nploye-d m@ay be the same as that conventiona@l@ly u- sed 2 5 fo r curing the polysu@lfide rlibber. It will -be tinde,i-stood th a,t,the amounts of blowin,.@ agent and of oxidizing curing a, ,en,t may vary with the polysulfide polymer uised and w ith the properties desired in the expanded rubber. T he polysulfide rubber compos-ition may also inrlude 3 0 ot he-r co-@mpounding ingredients suoh as carbon blac:k ' tita- ni um @dioxide, clays, or other fillers, as well as other com- p oundin,,- ingredients normally emp@loyed in the - formula- ti on of liquid polysulfide polymers. Al@thouqh heat is g enerally no,t required to effect the @ci-ire of -the polymer, 3 5 th e composition can be isubje!oted to modcrately elevated te impera,ttires (generally noit more than 1001 C.) in cases w here more rapid curinf. @ of the Tubber is desired. The d egree of ihe@ating, however, 'will be substantially less than th at required for ga@seous deicornpositio@n iof the blowing 4 0 a ge@n,ts in the absence of the oxidizing curatives - employed in @my process. Aetivators such as Iris (chmethylamino- m ethy@1) phenol or diphenyl guanidine rnay be emp,loyed. A cidic substances such ias stearic aeid, for example, func- ti on as oure retaa7ders, paxticulatly in the leiad dioxide cure. 4 5 A varie,ty of oxidizing curatives miay be used, the pre- fe rred material depending upon the type of hquid poly- s ulfide r@a-bber used, the itime of cure desired, land upon th e,color requirements to bemet. Typical cuting. agents 5 0 in c,lude lead @dioxide, cumenehydroperoxide, tellurium di- o xide and io(hne. Otlicr ouratives @such as quinone di- o xime, @2,4,6-trinitrobenzene, m-dinitrobenzene, etc.., may b e used- generally in the presence of activators such as d, iphenylgu,anidine, isulfur, etc. In ,@eneral, basic sub- @@Vances such as tri (dirtiethylamino methyl) phenol 5 5 ("

DMP-30") @activate .the ctire whereas acidic subs@tances @tend to retard the,cure. D@riers slich as lead octoate land m anganese or coba-lt salts are useful in the curing of the p olysulfide rubber. If desired, combinations of oxidizing a g@-nts may be einiployed to give the desired oharaoteri,ti,, 6 0 to the expanded product. -Incorp@oration of o@her poly- m eric substances such as epoxy resins, buta diene-acrylo- ni trile polymers, phenolic resins, and so fortb, may be de- si rab,le to impart special properties to the produot. Com- bi nations of different types of polysulfide rubbers w;ill 6 5 p, resent advantages in certain applications. T he following examples, in which all parts and percent- a. -es aTe expressed by weight, wiH serve to illustrate tb-, p ractice of th.-,lnvention in more deta@il. E xample 1 7 0 T he polysulfide ruibber employed in this and subsequent e xam,p,les was;acondens,,ition prodLTot of 98 niole-percent bi s-be,t@a-cbloroethyl formal and 2 mole-percent of 1,2,3- trichloropropaiie witb goi @-m _u , polysulfide, having an equiv- 75 4 alent weight of 1710 by m:froaptan end group analysis, andha@ving,a viscosity @f 560 poises -at 30' C. as measured by means of ja Birookfieild viscometer. Such,a liquid materi@al is -commercially ava-ilable unde-r the name "Thiokol LP-2." 100 p,arts of the foregoing polymer was mixed with 3,0 parts of semi-reinforcing carbon black ("Pelletex") and I part of stearic:acid, To 50 g. of this mixture was added 0. I g. (0.2 'Yo) of finely divided calcium hydride poivder. The materials were well mixed and -then 5 g. of a paste consisting of 50% I@ead pc@roxide, 45% dibutyl p(@Ahalate land 5Vo stea;ricacid was thoroughly blended in. Such a paste is commercially ianailable under the, name "Thiokol Accelerator C-@5." The mixtu@re was allowed to sband overnight at room temperature. A well expanded solid i7abbery product was obtained which gave la measured density of 0.84 g. per cc. A sinlilarly prep-ared sample containin.- .05 g. of mlcium hydride powder)slhowed a some,",h@at hligher density (0.92 g./ce.). A sample prepared in a similar manner with no blow@ing agent bad 'a densityof 1.28. Example 2 s One-ten@th ig. of odium borohydride was addedto 50 g. of T@hiokol LP-2 polymer,andthe composition wasthorougli4y blended with 5 g. of Thiokol Accelerator C-5. The mixture after standing -at room temperature overnight had;cured to a well expanded rubbery produet hav- in,g a density of 0.64 g. per ec. Si@rm 'lar preparataons made with 0.05 g. sodium borohydride and with 0.02 9. of sodium borohydride eac)h -gave -a well expanded rubbery prodliet showing densities of 0.67 and 0.82, respec- tively. Exan7ple 3 0 e@tenth of powdered ea-Icium hydride was mixed inf n @o 50 g. of Tbiokol LP-2 liquid pol@ynier. Five g. of Thiokol Acce.,I,-Pator C-5 was blended in and the MiXtuTe was allowed to stand; iroom temperature for thirty minutes. @-it was then placed in :an oven (at 70' C. for one at @P@our' An expanded,and cured rtibbery produc-t was obtainedwhichshowedaderisityofO.81g.percc. Inasim- ilar experiment in which the calcium hydride was replaced with one-tenth g. of sodium borohydride, the idensity of the product after 1/2 hour at 70' C. was 0.77. Exainple 4 one-tenth g. of sodium borohydride was added to 50 g. Thiokol LP-2 liquid polynier. After thorough mixing 5.0 g. of tellurium dioxide was blended in. The mixture was placed in a 70' C. oven for two hours, A well expanded, cured rubber was obtained (d=0.69). Example 5 One-tenth g. of powdered calcium hydride was mixed with 50 g. of Thiokol LP-2 liqtiid polymer. Then six 9. of cumene hydroperoxide and twenty-two drops of dimethyl amino methyl phenol (DMP-30) were anixed into the viscous fluid composition. After standing at room temperature overnight a well expanded light colored soft rubber sponge was obtained which had la density of 0.47. In an exactly similar experiment using 0.25 g. of powdered calcium hydride in place of the 0.1 g. used above, a soft, cellular rubbery product was obtained whiich had a density of O@.35. A sample prepared with no blowing agent but otherwise sirililar was not expanded and had a density of 1.16. Example 6 One-quarter g. of a 50% dispersion of sodium hydride in oil was added to 50 g. of Thiokol LP-2 liquid polymer. To the well blended mixture was added six g. of dicumyl peroxide and 22 drops of dimelhylamino methyl phenol ("DMP-30"). After thorough blending the mixture was allowed to stand overnight at room temperature. A well expanded c-ured rubbery product was obtained which had a den&ity of 0.62.

6. Document ID: US 2539848 A

L8: Entry 6 of 6 File: USOC Jan 30, 1951

DOCUMENT-IDENTIFIER: US 2539848 A
TITLE: Procaine urea

OCR Scanned Text (1):
Patented !an. 30, 1951 295399848 UNITED' STATES PATENT OFFICE 2,53@,848 PROCAINE UREA Ralph N. Lulek, Rosebank, N. Y., assignor to Hey- den Chemical Corporation, New York, N. Y., a corporation of Delaware No Drawing. Application December 8,1948, Serial No. 64,241 4 Claims. (Cl. 260-472) My invention relates particularly to procaine, or novocaine, derivatives and tl,,e process of producing the same. An object of my inve-Lition is to produce such derivatives, also more particularly to obtain modified forms of the well known drug novocaine, such as the Ilitherto unknowil procaine urea (Cl3HI902N2) 2CO, which is useful also in making procaine urea salicylate, a modified form of said drug novocaine providing a source of salicylic acid used in treating ulcers, Therapeutics, Materia Medica and Pharmacy, Patter, 13th ed., 1917, page 862, L. Blakiston's Sons & Co., Phila., Pa. The object is, also, to provide new chemical compounds and to advance the art accordingly. While my invention may have many different embodiments and may be carried out in many different ways, for the purpose of illustration I have described hereinafter only certain examples thereof. For example, in making procaine urea (Cl3I-1i9O2N2) 2CO which may be expressed as 0 El 0 H 1 1-11-1 2 Of procaine urea. The product obtained melts at aboiit 135-136' C. It will be understood, however, that the proportions of pyridine and ethyl acetate can vary through any desired wide limits. Instead of ethyl acetate I may substitute any other suitable solvents, as for instance acetone, isopropylacetate, etc. Also, the temperature may be varied between 1.5' and 75' C., as desired, for the reaction. 10 Instead of pyridine I may substitute, for example, quinoline or dimethyl aniline. In making procaine urea salicylate, which may be expressed as (C13HI902N2)2CO(C71-1603)2, I may proceed as follows, for example: 15 A solution of 13.8 grams of salicylic acid in 50 grams of ethanol, having a strength of 95%, is added to an ethanol solution of 25 grams of said procaine urea containing 30 grams of ethanol of 20 95% strength. When the alcohol has been re- moved by dis@illati-On the oil remaining solidifies on standing. This solid is recrystallized from ether-methanol coiiaprising 200 cc. of ether and 200 cc. of methanol and then air dried. The yield 25 of procaine urea salicylate is 91.5 %, based on the 0 11 (C2H5)2NCH2CH20-@-<=>-N C N-<:D-C-OCH2CH2N (C2H5)2 which is di-(g-diethylamino) ethyl ester of 4,4'- 3(procaine urea originally present. It melts at dicarboxy diphenyl urea or 4,4'-di-(p-diethyl- about 102-105' C. amino) carbethoxy diphenyl urea, I may proceed The proportions of the etbanol as above can be as follows: varied within wide limits, as desired. Also, in- Into a mixture of I liter of a tertiary base, such stead of ethanol I may substitute other alcohols, as pyridine, 1 liter of ethyl acetate, and 512 gratris 35 such as isopropanol, n-propanol, etc., and instead of procaine hydrochloride, that is to say novo- of the ether-methanol solution I may substitute caine hydrochloride substa ntially any other ether-alcohol mixture as a solvent. NH2 C02CH2CH2N(C2HB)2HOI While I have described my invention above in <:D 40 deta il it will be understood 'Lhat the same may be which is very soluble in water 9,nd used as a sub- varied without departing from the spirit of my stitute for cgcaine and as a lo.cal anaesthetic, inve ntion. Martin, Organic Chemistry, 3rd ed., 1917, page I claim: 604, Appleton & Company, New York, Thorpe, 1. A new chemical compound 4,4'- di-(,6-di- App. Chem., v. HI, page 718, 1916, is passed 100 45 ethylami no) carbethoxy diphenyl urea, having the grams of phosgene. The temperature of the mix-

following formula: 0 @H 0 H 0 1 1 1 1 1 (C2H5)2NCH2cH20-8-<:D-N-C-I-<::>C- OCH2CH2N (C2H5)2 ture is preferably held between 35' and 40' C. 60 2. The process which comprises reacting at a during the addition. Then the r.,iixture is chilled tempera ture between 15' and 75' C., procaine hy- to 151 C. and filtered, and the solid product ob- drochlori de with phosgene in the prese-,ice of a tained is recrystallized three times from 90% tertiary base to form procaine urea. strength ethanol, and once from 98% strength 3. The process vihich comprises reacting, at methqnol, to yield 50@,, of t]4e theoretie?a a d mpunt 55 %pqqt P5, to 401 C., procaine hy rophqride wi h t

Full | Title | Citation

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DATE: Friday, March 18, 2005

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,USOC; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L9	(FLVH or phe leu val his) same (d-amino acid? or D$amino or D-peptide or D$epptide or D-form?)	0
☐	L8	($1IAPP or islet beta amyloid?) same (d-amino acid? or D$amino or D-peptide or D$epptide or D-form?)	6
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☐	L6	(IAPP or islet beta amyloid?) smame (d-amino acid? or D$amino or D-peptide or D$epptide or D-form?)	0
☐	L5	6303567.pn.	1
☐	L4	amyloid same $peptide? same (D-form? or D-amino acid? or D4isomer?)	21
☐	L3	amyloid and (D-form? or D-amino acid? or D4isomer?)	358
☐	L2	findels and amyloid and (D-form? or D-amino acid? or D4isomer?)	0
☐	L1	findels and amyloid same (D-form? or D-amino acid? or D4isomer?)	0

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DATE: Friday, March 18, 2005

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			DB=PGPB,USPT,USOC; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L4		amyloid same $peptide? same (D-form? or D-amino acid? or D4isomer?)	21
☐	L3		amyloid and (D-form? or D-amino acid? or D4isomer?)	358
☐	L2		findels and amyloid and (D-form? or D-amino acid? or D4isomer?)	0
☐	L1		findels and amyloid same (D-form? or D-amino acid? or D4isomer?)	0

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Search Results - Record(s) 1 through 21 of 21 returned.

☐ 1. Document ID: US 20050059602 A1

L4: Entry 1 of 21 File: PGPB Mar 17, 2005

DOCUMENT-IDENTIFIER: US 20050059602 A1
TITLE: Peptides for the treatment of Alzheimer's disease and other beta-amyloid protein fibrillogenesis disorders

Detail Description Paragraph:
[0078] As used herein the laminin-derived polypeptides of the present invention may consist of -L amino acid, -D amino acids or a mixture of both forms. Amino acids in nature usually consist of -L amino acids. However, substitution with -D amino acids may demonstrate enhanced A.beta. amyloid inhibitory activity, enhanced bioavailability due to less degradation in biological fluids (such as plasma), and enhanced penetration across the blood-brain-barrier. Polypeptides having an identical amino acid sequence to that found within a parent peptide but which all or part of the L-amino acids have been substituted with D-amino acids is part of the present invention for the development of therapeutics to treat Alzheimer's disease and other A.beta. amyloidoses.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 20040214774 A1

L4: Entry 2 of 21 File: PGPB Oct 28, 2004

DOCUMENT-IDENTIFIER: US 20040214774 A1
TITLE: Prevention and treatment of Alzheimer amyloid deposition

Summary of Invention Paragraph:
[0010] One can speculate that selective ablation of the apoE effect on A.beta. could potentially have a therapeutic effect leading to reduced A.beta. deposition. ApoE hydrophobically binds to A.beta. forming SDS insoluble complexes (Stritttnatter et al., "Apolipoprotein E: High-avidity Binding to Beta-amyloid and Increased Frequency of Type 4 Allele in Late-onset Familial Alzheimer Disease," Proc. Natl. Acad. Sci. (USA) 90:1977-1981 (1993); Wisniewski et al., "Apolipoprotein E: Binding to Soluble Alzheimer's Beta-amyloid," Biochem. Biophys. Res. Commun. 192:359-365 (1993); Naslund et al. "Characterization of Stable Complexes Involving Apolipoprotein E and the Amyloid Beta Peptide in Alzheimer's Disease Brain," Neuron 15:219-228 (1995); which are hereby incorporated by reference in their entirety). Although the affinity of binding depends on A.beta. conformation (A.beta. soluble vs. fibrillar), the binding remains in the low

nanomolar range (Golabek et al., "The Interaction Between Apolipoprotein E and Alzheimer's Amyloid .beta.-peptide is Dependent on .beta.-peptide Conformation," J. Biol. Chem. 271:10602-10606 (1996); Strittmatter et al., "Apolipoprotein E: High-avidity Binding to Beta-amyloid and Increased Frequency of Type 4 Allele in Late-onset Familial Alzheimer Disease," Proc. Natl. Acad. Sci. (USA) 90:1977-1981 (1993); Golabek et al., "Amyloid .beta. Binding Proteins in vitro and In Normal Human Cerebrospinal Fluid," Neurosci. Lett. 191:79-82 (1995); Shuvaev et al., "Interaction Between Human Amphipathic Apolipoproteins and Amyloid .beta.-peptide: Surface Plasmon Resonance Studies," REBS Lett. 383:9-12 (1996); which are hereby incorporated by reference in their entirety). Prior studies identified residues 12-28 of A.beta. as the binding site for apoE binding on A.beta. (Golabek et al., "The Interaction Between Apolipoprotein E and Alzheimer's Amyloid .beta.-peptide is Dependent on .beta.-peptide Conformation," J. Biol. Chem. 271:10602-10606 (1996); Strittmatter et al., "Apolipoprotein E: High-avidity Binding to Beta-amyloid and Increased Frequency of Type 4 Allele in Late-onset Familial Alzheimer Disease," Proc. Natl. Acad. Sci. (USA) 90:1977-1981 (1993); Ma et al., "Alzheimer A.beta. Neurotoxicity: Promotion by Antichymotrypsin, ApoE4; Inhibition by A.beta.-related Peptides," Neurobiol. Aging 17:773-780 (1996); which are hereby incorporated by reference in their entirety). Hence, synthetic peptide homologues to residues 12-28 of A.beta. can be used as competitive agonists of the binding of full length A.beta. to apoE. However, A.beta.12-28 is known to be fibrillogenic and can be associated with toxicity (Gorevic et al., "Ten to Fourteen Residue Peptides of Alzheimer's Disease Protein are Sufficient for Amyloid Fibril Formation and its Characteristic S-ray Diffraction Pattern," Biochem. Biophys. Res. Commun. 147:854-862 (1987), which is hereby incorporated by reference in its entirety). Therefore, the A.beta.12-28 sequence has been modified by substitution of the valine at residue 18 to proline, rendering this peptide non-fibrillogenic and non-toxic. Substitutions of valine at residue 18 can also be with other amino acids which render the peptide non-toxic. Further modifications include using D-amino acids, amidation of the C-terminus, and acetylation of the N-terminus in order to extend the serum half-life of the peptide. In a series of experiments, the effect of pharmacological blockade of apoE's pathological chaperoning properties on A.beta. fibrillogenesis and toxicity was examined in vitro using A.beta.12-28 and A.beta.12-28P. A.beta.12-28P was also administered to AD Tg mice to investigate the in vivo effect of blocking the apoE/A.beta. interaction on amyloid deposition.

Detail Description Paragraph:

[0062] In order to minimize degradation by endogenous peptidases and extend the half-life, A.beta.12-28P (and A.beta.12-28 as a control) were synthesized using D-amino acids and were end protected by amidation of the C-terminus and acetylation of the N-terminus. A.beta.12-28P and A.beta.12-28 used for all in vitro and in vivo experiments originated from the same batch of large scale peptide synthesis. Details of synthesis, purification, and sequence verification were described previously (Sigurdsson et al., "In vivo Reversal of Amyloid .beta. Lesions in Rat Brain," J. Neuropath. Exp. Neurol. 59:11-17 (2000); Sigurdsson et al., "Immunization with a Nontoxic/Nonfibrillar Amyloid-.beta. Homologous Peptide Reduces Alzheimer's Disease Associated Pathology in Transgenic Mice," Am. J. Pathol. 159:439-447 (2001); Matsubara et al., "Apolipoprotein J and Alzheimer's Amyloid .beta. Solubility," Biochem. J. 316:671-679 (1996); which are hereby incorporated by reference in their entirety). For aggregation studies and assessment of secondary structure, the peptides were initially diluted in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP; Sigma, St. Louis, Mo.) at a concentration of 10 mM/ml, aliquoted and lyophilized. HFIP treatment renders peptides monomeric with minimal .beta.-sheet content (Stine et al., "In vitro Characterization of Conditions for Amyloid-beta Peptide Oligomerization and Fibrillogenesis," J. Biol. Chem. 278:11612-11622 (2003), which is hereby incorporated by reference in its entirety). Lyophilized peptides were stored at -80.degree. C. and resuspended immediately prior to each experiment in the appropriate diluent. For in vivo experiments, a 1 mg/ml stock solution of A.beta.12-28P was prepared in 50% acetonitrile containing 0.1% trifluoroacetic acid which was aliquoted, lyophilized,

and stored at -80.degree. C. until use.

Detail Description Paragraph:
[0065] The fibrillogenic potential of A.beta.12-28 and A.beta.12-28P was investigated using a Thioflavin-T assay according to previously published methods (Wisniewski et al., "Acceleration of Alzheimer's Fibril Formation by Apolipoprotein E in vitro," Am. J. Pathol. 145:1030-1035 (1994); Castano et al., "Fibrillogenesis in Alzheimer's Disease of Amyloid Beta Peptides and Apolipoprotein E," Biochem. J. 306:599-604 (1995); which are hereby incorporated by reference in their entirety). A.beta.1-40 and A.beta.1-42 were studied for comparison. A.beta.12-28 and A.beta.12-28P used for these experiments were both synthesized from D-amino acids to avoid effect of different racemic conformers on the fibril formation. All peptides were HFIP treated and reconstituted in 100 mM Tris buffer (pH 7.4) to obtain a 100 .mu.mol/L concentration. A.beta.1-40 or A.beta.1-42 (100 .mu.mol/L) were also incubated in the presence of 1 .mu.mol/L of apoE3 or E4. In aggregation, inhibition experiments, apoE3 or E4 were preincubated with A.beta.12-28 or A.beta.12-28P in a ratio 1:2 for 6 h at 37.degree. C. and then added to instantly reconstituted A.beta.1-40 or A.beta.1-42. Peptides were incubated over a period of 10 days at 37.degree. C. Samples containing 15 .mu.g of incubated peptides were taken at indicated intervals and fluorescence was measured as previously described in a Perkin-Elmer LS-50B fluorescence spectrophotometer (Perkin Elmer Instruments, Shelton, Conn.) (Wisniewski et al., "Acceleration of Alzheimer's Fibril Formation by Apolipoprotein E in vitro," Am. J. Pathol. 145:1030-1035 (1994); Golabek et al., "The Interaction Between Apolipoprotein E and Alzheimer's Amyloid .beta.-peptide is Dependent on .beta.-peptide Conformation," J. Biol. Chem. 271:10602-10606 (1996); which are hereby incorporated by reference in their entirety). The mean.+-.standard deviation ("SD") for three separate experiments was plotted in FIG. 1. Differences in amount of fibrils formed by the different peptides were evaluated by means of a repeated measures ANOVA, followed by a Tukey HSD post-hoc test using Statistica (version 6.1) (StatSoft Inc., Tulsa, Okla.).

Detail Description Paragraph:
[0088] Accumulation of A.beta.3, a 39-43 amino acid peptide, in brains of AD patients is a hallmark of AD pathology (Selkoe, "The Origins of Alzheimer Disease: A is for Amyloid," JAMA 283:1615-1617 (2000), which is hereby incorporated by reference in its entirety). Complementary pieces of evidences derived from in vivo and in vitro studies have demonstrated that apoE critically promotes A.beta. fibrillization and deposition (Wisniewski et al., "Acceleration of Alzheimer's Fibril Formation by Apolipoprotein E in vitro," Am. J. Pathol. 145:1030-1035 (1994); Bales et al., "Lack of Apolipoprotein E Dramatically Reduces Amyloid .beta.-peptide Deposition," Nature Gen. 17:263-264 (1997); Ma et al., "Alzheimer A.beta.3 Neurotoxicity: Promotion by Antichymotrypsin, ApoE4; Inhibition by A.beta.-related Peptides," Neurobiol. Aging 17:773-780 (1996); Bales et al., "Apolipoprotein E is Essential for Amyloid Deposition in the APPV717F Transgenic Mouse Model of Alzheimer's Disease," Proc. Natl. Acad. Sci. (USA) 96:15233-15238 (1999); Holtzman et al., "Apolipoprotein E Isoform-dependent Amyloid Deposition and Neuritic Degeneration in a Mouse Model of Alzheimer's Disease," Proc. Natl. Acad. Sci. (USA) 97:2892-2897 (2000), which are hereby incorporated by reference in their entirety). The most striking example, emphasizing role of apoE as a pathological chaperone of .beta.-amyloidosis, comes from experiments with generation of APP.sup.V.sup.717F/apoE.sup.-/- mice which have a delayed onset of A.beta. deposition, a reduced A.beta. load, and no fibrillar A.beta. deposits, compared to APP.sup.V717F/apoE.sup.+/+ Tg mice. APP.sup.V717F/apoE.sup.+/- mice demonstrate an intermediate level of pathology (Bales et al., "Lack of Apolipoprotein E Dramatically Reduces Amyloid .beta.-peptide Deposition," Nature Gen. 17:263-264 (1997); Bales et al., "Apolipoprotein E is Essential for Amyloid Deposition in the APPV717F Transgenic Mouse Model of Alzheimer's Disease," Proc. Natl. Acad. Sci. (USA) 96:15233-15238 (1999); Holtzman et al., "Expression of Human Apolipoprotein E Reduces Amyloid-beta Deposition in a Mouse Model of Alzheimer's Disease," J. Clin. Invest. 103:R15-R21 (1999); Holtzman et al., "Apolipoprotein E Isoform-dependent

Amyloid Deposition and Neuritic Degeneration in a Mouse Model of Alzheimer's Disease," Proc. Natl. Acad. Sci. (USA) 97:2892-2897 (2000), which are hereby incorporated by reference in their entirety). Neutralization of the chaperoning effect apoE would therefore potentially have a mitigating effect on A.beta. accumulation; however, evidence also suggests that apoE has a role in the clearance of A.beta. peptides (Rebeck et al., "Multiple, Diverse Senile Plaque-associated Proteins are Ligands of an Apolipoprotein E Receptor, the Alpha 2-Macroglobulin Receptor/Low-density-lipoprotein Receptor-related Protein," Ann. Neurol. 37:211-217 (1995); LaDu et al., "Apolipoprotein E Receptors Mediate the Effects of .beta.-amyloid on Astrocyte Cultures," J. Biol. Chem. 275:33974-33980 (2000); Ji et al., "Amyloid .beta.40/42 Clearance Across the Blood-brain Barrier Following Intra-ventricular Injections in Wild-type, ApoE Knock-out and Human apoE3 or E4 Expressing Transgenic Mice," J. Alz. Dis. 3:23-30 (2001); DeMattos et al., "ApoE and Clusterin Cooperatively Suppress A.beta. Levels and Deposition. Evidence that apoE Regulates Extracellular A.beta. Metabolism in vivo," Neuron 41:193-202 (2004); which are hereby incorporated by reference in their entirety), as well as other important functions for neuronal maintenance (Nathan et al., "Differential Effects of Apolipoproteins E3 and E4 on Neuronal Growth in vitro," Science 264:850-852 (1994); Ji et al., "Apolipoprotein E4 Potentiates Amyloid .beta. Peptide-induced Lysosomal Leakage and Apoptosis in Neuronal Cells," J. Biol. Chem. 277:21821-21828 (2002); Buttini et al., "Modulation of Alzheimer-like Synaptic and Cholinergic Deficits in Transgenic Mice by Human Apolipoprotein E Depends on Isoform, Aging and Overexpression of Amyloid .beta. Peptides but not on Plaque Formation," J. Neurosci. 22:10539-10548 (2002); Teter et al., "Role of Apolipoprotein E and Estrogen in Mossy Fiber Sprouting in Hippocampal Slice Cultures," Neuroscience 91:1009-1016 (1999); Ji et al., "Apolipoprotein E Isoform-specific Regulation of Dendritic Spine Morphology in Apolipoprotein E Transgenic Mice and Alzheimer's Disease Patients," Neurosci. 122:305-315 (2003); which are hereby incorporated by reference in their entirety), therefore it is difficult to predict a priori the in vivo effect of inhibiting the apoE/A.beta. interaction. In order to investigate this possible therapeutic mechanism, a peptide homologous to residues 12-28 of A.beta. was synthesized, which is the apoE binding domain (Golabek et al., "The Interaction Between Apolipoprotein E and Alzheimer's Amyloid .beta.-peptide is Dependent on .beta.-peptide Conformation," J. Biol. Chem. 271:10602-10606 (1996); Strittmatter et al., "Apolipoprotein E: High-Avidity Binding to Beta-amyloid and Increased Frequency of Type 4 Allele in Late-onset Familial Alzheimer Disease," Proc. Natl. Acad. Sci. (USA) 90:1977-1981 (1993); Ma et al., "Alzheimer A.beta. Neurotoxicity: Promotion by Antichymotrypsin, ApoE4; Inhibition by A.beta.-related Peptides," Neurobiol. Aging 17:773-780 (1996); which are hereby incorporated by reference in their entirety). Such peptide can act as a competitive inhibitor of the apoE/full length A.beta. interaction. To avoid the intrinsic toxicity associated with a residual capacity to form fibrils (Gorevic et al., "Ten to Fourteen Residue Peptides of Alzheimer's Disease Protein are Sufficient for Amyloid Fibril Formation and its Characteristic s-ray Diffraction Pattern," Biochem. Biophys. Res. Commun. 147:854-862 (1987), which is hereby incorporated by reference in its entirety), and hence the ability to co-deposit on existing plaques, the sequence of A.beta.12-28 was modified by replacing valine for proline in position 18. This renders A.beta.12-28P non-fibrillogenic as demonstrated using circular dichroism and Thioflavin-T assays, as well as being non-toxic in cell culture studies. These modifications did not abolish the affinity of A.beta.12-28P to apoE. On a competitive inhibition assay, A.beta.12-28P bound to apoE, preventing its interaction with full length A.beta. immobilized on a solid phase (IC.sub.50=36.7 nM). The effect of apoE on A.beta. fibril formation and toxicity in cell culture was significantly reduced in the presence of A.beta.12-28P. The use of A.beta.12-28P, synthesized with end-protection and using D-amino acids, allowed extension of its half-life in the serum to 62 min. A.beta.12-28P is BBB permeable, making it potentially useful as a CNS agent in vivo. APP.sup.K670N/M671L/PS1.sup.M146L AD Tg mice treated with A.beta.12-28P, demonstrated a significantly lower A.beta. load, resembling the situation observed in mice with decreased apoE expression (Bales et al., "Lack of Apolipoprotein E Dramatically Reduces Amyloid .beta.-peptide

Deposition," Nature Gen. 17:263-264 (1997); Bales et al., "Apolipoprotein E is Essential for Amyloid Deposition in the APPV717F Transgenic Mouse Model of Alzheimer's Disease," Proc. Natl. Acad. Sci. (USA) 96:15233-15238 (1999); Holtzman et al., "Expression of Human Apolipoprotein E Reduces Amyloid-beta Deposition in a Mouse Model of Alzheimer's Disease," J. Clin. Invest. 103:R15-R21 (1999); Holtzman et al., "Apolipoprotein E Isoform-dependent Amyloid Deposition and Neuritic Degeneration in a Mouse Model of Alzheimer's Disease," Proc. Natl. Acad. Sci. (USA) 97:2892-2897 (2000); which are hereby incorporated by reference in their entirety). The initial A.beta. plaques in APP.sup.K670N/M671L/PS1.sup.M146L mice appear at three months of age; whereas, between the fourth and the fifth months of life, A.beta. deposition follows an exponential curve where new plaques are actively formed and soluble A.beta. co-deposits on existing lesions (Wengenack et al., "Quantitative Histological Analysis of Amyloid Deposition in Alzheimer's Double Transgenic Mouse Brain," Neurosci. 101:939-944 (2000), which is hereby incorporated by reference in its entirety). It is shown herein that administration of A.beta.12-28P for a period as short as one month resulted in a reduction in A.beta. load, and plaque density over two fold compared to untreated age matched Tg animals. Treated mice showed a decreased density of plaques of all sizes, suggesting that blocking the role of apoE as a pathological chaperone of A.beta. prevents formation of new plaques as well as growth of already existing lesions. This occurs in an absence of a humoral response since no anti-A.beta. antibodies were detected in the sera of treated animals.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 3. Document ID: US 20040185038 A1

L4: Entry 3 of 21 File: PGPB Sep 23, 2004

DOCUMENT-IDENTIFIER: US 20040185038 A1
TITLE: Methods for reducing immunogenicity of polypeptides

Detail Description Paragraph:
[0081] Thus U.S. Pat. No. 5,985,242 discloses synthetic beta-amyloid peptide analogues featuring D-amino acids which are proposed to bind the naturally occurring beta-amyloid peptide component of the nascent neurofibrilary tangles present in amyloidogenic diseases such as Alzheimers disease. By so binding, the peptide analogues inhibit further aggregation. Similarly, peptide analogues of human myelin basic protein (MBP) containing D-amino acids have been described. In one embodiment of U.S. Pat. No. 5,948,764 peptides of at least 7 amino acids and preferably encompassing residues 86-99 of the human MBP are described. Peptides including residue 87 which would otherwise be an L-valine are modified to include a D-amino acid at this position such that the peptide analogue achieves increased binding to MHC relative to the native MBP 87-99. A typical modification will include L-valine to D-valine or another D-amino acid.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 4. Document ID: US 20040157781 A1

L4: Entry 4 of 21 File: PGPB Aug 12, 2004

DOCUMENT-IDENTIFIER: US 20040157781 A1
TITLE: Peptide binding the KLVFF-sequence of amyloid-beta

Detail Description Paragraph:
[0102] In an additional series of experiments, it was demonstrated that KLVFF binds stereo specifically to the homologous sequence in AS (i.e. A.beta.-16-20). By screening combinatorial pentapeptide libraries exclusively composed of D-amino acids (lowercase) with labelled KLVFF, several ligands with a motif containing phenylalanine (f) in the second and leucine (l) in the third position were identified (e.g. lflrr). By using a short peptide in the screening, known to bind to a region in A.beta. critical for its polymerization (i.e. KLVFF), the risk of identifying D-pentapeptides that interact with nonrelevant regions in A.beta. (N- or C-terminal to A.beta.-16-20) was eliminated. Like KLVFF, the D-amino acid ligands were found not only to bind to A.beta. but also to inhibit amyloid fibril formation. Since peptides built up of D-amino acids are resistant to proteolytic degradation, these ligands may be beneficial for inhibition of amyloidogenesis in vivo. The results further indicate that KLVFF will be useful in the identification of small organic molecules (e.g. by screening of substance libraries) with the ability to bind to A.beta. in this relevant region and inhibit amyloid fibril formation (candidate drugs for the treatment of Alzheimer disease and other related amyloidoses).

[ ] 5. Document ID: US 20030236197 A1

L4: Entry 5 of 21 File: PGPB Dec 25, 2003

DOCUMENT-IDENTIFIER: US 20030236197 A1
TITLE: Modulators of beta-amyloid peptide aggregation

Summary of Invention Paragraph:
[0008] This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural .beta.-APs. The compounds are modified in a manner which allows for increased biostability and prolonged elevated plasma levels. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is an inverso isomer of an L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP, or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO:4). In preferred embodiments, a phenylalanine in the compounds of the invention is. substituted with a phenylalanine analogue which is more stable and less prone to, for example, oxidative metabolism, or allows for increased brain levels of the compound.

Summary of Invention Paragraph:
[0009] In yet another embodiment, a modulator compound of the invention includes a .beta.-amyloid peptide comprised of D-amino acids, L-amino acids or both, an inverso isomer of a .beta.-amyloid peptide, or a retro-inverso isomer of a .beta.-amyloid peptide which is attached to a hydrazine moiety, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides.

Detail Description Paragraph:
[0028] As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect and/or may improve the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (e.g., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found within a parent peptide but in which all L-amino acids have been substituted with all D-amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detail Description Paragraph:
[0029] As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D-Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman et al "Perspectives in Peptide Chemistry" pp. 283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detail Description Paragraph:
[0032] In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In preferred embodiments, a phenylalanine in the compounds of the invention is substituted with a phenylalanine analogue which is more stable and less prone to, for example, oxidative metabolism.

Detail Description Paragraph:
[0034] In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In preferred

embodiments, the phenylalanines in the compounds of the invention are substituted with phenylalanine analogues which are more stable and less prone to, for example, oxidative metabolism.

Detail Description Paragraph:
[0036] In yet another embodiment, a modulator compound of the invention includes a .beta.-amyloid peptide comprised entirely or partially of D-amino acids, an inverso isomer of a .beta.-amyloid peptide, or a retro-inverso isomer of a .beta.-amyloid peptide which is attached to a hydrazine moiety, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the modulator compound of the invention is comprised of 1-20 D-amino acids, more preferably 1-10 D-amino acids, even more preferably 1-5 D-amino acids, and most preferably 2-4 D-amino acids which are attached to a hydrazine moiety.

6. Document ID: US 20030186946 A1

L4: Entry 6 of 21 File: PGPB Oct 2, 2003

DOCUMENT-IDENTIFIER: US 20030186946 A1
TITLE: Suppression of cytotoxic protein conformers

Summary of Invention Paragraph:
[0021] U.S. Pat. No. 6,277,826 issued on Aug. 21, 2001 to Findeis, et al. for "Modulators of .beta.-amyloid peptide aggregation comprising .beta.-amino acids" is said to relate to peptides comprised entirely of D-amino acids that modulate natural .beta. amyloid peptide aggregation. The peptides are said to be preferably based on a .beta. amyloid peptide, and preferably comprise 3-5 D-amino acid residues and include at least two D-amino acid residues independently selected from D-leucine, D-phenylalanine and D-valine. In a particularly preferred embodiment, the patent states that the peptide is a retro-inverso isomer of a .beta. amyloid peptide, and that in certain embodiments the peptide is modified at the amino-terminus, the carboxy-terminus, or both. Preferred amino-terminal modifying groups are said to include cyclic, heterocyclic, polycyclic and branched alkyl groups, and preferred carboxy-terminal modifying groups are said to include an amide group, an alkyl amide group, an aryl amide group or a hydroxy group. See also U.S. Pat. No. 6,303,567 issued on Oct. 16, 2001 to Findeis, et al. for "Modulators of .beta.-amyloid peptide aggregation comprising D-amino acids"

7. Document ID: US 20030114510 A1

L4: Entry 7 of 21 File: PGPB Jun 19, 2003

DOCUMENT-IDENTIFIER: US 20030114510 A1
TITLE: Treatments for neurotoxicity in alzheimer's disease

Detail Description Paragraph:
[0049] Preferably, peptide-based compounds are non-hydrolyzable. To provide such peptide compounds, one may select peptides from a library of non-hydrolyzable peptides, such as peptides containing one or more D-amino acids or peptides containing one or more non-hydrolyzable peptide bonds linking amino acids. Alternatively, one can select peptides which are optimal for disrupting .beta.-amyloid peptide aggregation, calcium influx and/or membrane depolarization and then modify such peptides as necessary to reduce the potential for hydrolysis by proteases. For example, to determine the susceptibility to proteolytic cleavage, peptides may be labeled and incubated with cell extracts or purified proteases and then isolated to determine which peptide bonds are susceptible to proteolysis, e.g., by sequencing it peptides and proteolytic fragments. Alternatively, potentially susceptible peptide bonds can be identified by comparing the amino acid sequence of a peptide with the known cleavage site specificity of a panel of proteases. Based on the results of such assays, individual peptide bonds which are susceptible to proteolysis can be replaced with non-hydrolyzable peptide bonds by in vitro synthesis of the peptide. Many non-hydrolyzable peptide bonds are known in the art, along with procedures for synthesis of peptides containing such bonds. Non-hydrolyzable bonds include -psi[CH.sub.2NH]-- reduced amide peptide bonds, -psi [COCH.sub.2]-- ketomethylene peptide bonds, -psi[CH(CN)NH]-- (cyanomethylene)amino peptide bonds, -psi[CH.sub.2CH(OH)]-- hydroxyethylene peptide bonds, -psi [CH.sub.2O]-- peptide bonds, and -psi[CH.sub.2S]-- thiomethylene peptide bonds.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 8. Document ID: US 20030105152 A1

L4: Entry 8 of 21 File: PGPB Jun 5, 2003

DOCUMENT-IDENTIFIER: US 20030105152 A1
TITLE: Treatments for neurotoxicity in Alzheimer's disease

Detail Description Paragraph:
[0048] Preferably, peptide-based compounds are non-hydrolyzable. To provide such peptide compounds, one may select peptides from a library of non-hydrolyzable peptides, such as peptides containing one or more D-amino acids or peptides containing one or more non-hydrolyzable peptide bonds linking amino acids. Alternatively, one can select peptides which are optimal for disrupting .beta.-amyloid peptide aggregation, calcium influx and/or membrane depolarization and then modify such peptides as necessary to reduce the potential for hydrolysis by proteases. For example, to determine the susceptibility to proteolytic cleavage, peptides may be labeled and incubated with cell extracts or purified proteases and then isolated to determine which peptide bonds are susceptible to proteolysis, e.g., by sequencing peptides and proteolytic fragments. Alternatively, potentially susceptible peptide bonds can be identified by comparing the amino acid sequence of a peptide with the known cleavage site specificity of a panel of proteases. Based on the results of such assays, individual peptide bonds which are susceptible to proteolysis can be replaced with non-hydrolyzable peptide bonds by in vitro synthesis of the peptide.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

9. Document ID: US 20030013648 A1

L4: Entry 9 of 21 File: PGPB Jan 16, 2003

DOCUMENT-IDENTIFIER: US 20030013648 A1
TITLE: Peptides for the treatment of Alzheimer's disease and other beta-amyloid protein fibrillogenesis disorders

Detail Description Paragraph:
[0078] As used herein the laminin-derived polypeptides of the present invention may consist of -L amino acid, -D amino acids or a mixture of both forms. Amino acids in nature usually consist of -L amino acids. However, substitution with -D amino acids may demonstrate enhanced A.beta. amyloid inhibitory activity, enhanced bioavailability due to less degradation in biological fluids (such as plasma), and enhanced penetration across the blood-brain-barrier. Polypeptides having an identical amino acid sequence to that found within a parent peptide but which all or part of the L-amino acids have been substituted with D-amino acids is part of the present invention for the development of therapeutics to treat Alzheimer's disease and other A.beta. amyloidoses.

10. Document ID: US 20020142950 A1

L4: Entry 10 of 21 File: PGPB Oct 3, 2002

DOCUMENT-IDENTIFIER: US 20020142950 A1
TITLE: Methods for enhancing the bioavailability of a drug

Detail Description Paragraph:
[0073] In another embodiment, a .beta.-amyloid peptide derivative of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the .beta.-amyloid peptide derivative binds to P-glycoprotein and inhibits its function and/or binds natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide derivative is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the retro-inverso isomer is amino-terminally modified, for example with a modifying group comprising an alkyl group such as a C1-C6 lower alkyl group, or a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the retro-inverso isomer is carboxy-terminally modified, for example with an amide group, an alkyl or aryl amide group (e.g., phenethylamide) or a hydroxy group (i.e., the reduction product of a peptide acid, resulting in a peptide alcohol). Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The retro-inverso isomer may be modified to enhance the ability of the .beta.-amyloid peptide derivative to inhibit P-glycoprotein and/or cytochrome P450 function, and/or to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, the retro-inverso isomer may be

modified to alter a pharmacokinetic property of the .beta.-amyloid peptide derivative and/or to label the .beta.-amyloid peptide derivative with a detectable substance (described further in subsection III below).

11. Document ID: US 20020103134 A1

L4: Entry 11 of 21 File: PGPB Aug 1, 2002

DOCUMENT-IDENTIFIER: US 20020103134 A1
TITLE: Modulators of beta-amyloid peptide aggregation comprising D-amino acids

Summary of Invention Paragraph:
[0008] This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural .beta.-APs. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO: 3).

Detail Description Paragraph:
[0033] As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (e.g., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found within a parent peptide but in which all L-amino acids have been substituted with all D-amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detail Description Paragraph:
[0034] As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D-Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the

side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman et al "Perspectives in Peptide Chemistry" pp. 283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detail Description Paragraph:
[0037] In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the .beta.-amyloid peptide of the modulator is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the .beta.-amyloid peptide of the modulator is carboxy-terminally modified, for example the modulator can comprise a peptide amide, a peptide alkyl or aryl amide (e.g., a peptide phenethylamide) or a peptide alcohol. Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The .beta.-amyloid peptide of the modulator may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, .beta.-amyloid peptide of the modulator may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detail Description Paragraph:
[0038] In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the retro-inverso isomer is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the retro-inverso isomer is carboxy-terminally modified, for example with an amide group, an alkyl or aryl amide group (e.g., phenethylamide) or a hydroxy group (i.e., the reduction product of a peptide acid, resulting in a peptide alcohol). Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The retro-inverso isomer may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, the retro-inverso isomer may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detail Description Paragraph:
[0163] In this example, the necessity for an N-terminal modifying group on the D-amino acid-based modulator compounds was evaluated. Peptides comprised entirely of D-amino acids and having a free amino terminus were prepared and tested for their ability to inhibit aggregation of natural .beta.-amyloid peptide using aggregations assays as described in Example 2. Abbreviations used in this example and presentation of the data are the same as described in Example 3. The results are shown below in Table VI. Compounds exhibiting a change in lag time (.DELTA.Lag) of 1.3 or greater are highlighted in bold.

Detail Description Paragraph:

[0164] The results shown in Table VI demonstrate that modulators comprising all D-amino acids and having a free amino terminus are effective at inhibiting aggregation of natural .beta.-amyloid peptides (i.e., an N-terminal modifying group is not required for the D-amino acid-containing modulators to effectively inhibit aggregation of natural .beta.-amyloid peptides). A particularly preferred D-amino acid modulator compound having a free amino-terminus is PPI-579, the retro-inverso isomer of A.beta..sub.17-21 (A.sub.21.fwdarw.F) with a C-terminal amide.

12. Document ID: US 20020094957 A1

L4: Entry 12 of 21 File: PGPB Jul 18, 2002

DOCUMENT-IDENTIFIER: US 20020094957 A1
TITLE: Peptide binding the KLVFF-sequence of amyloid-beta

Detail Description Paragraph:
[0097] In an additional series of experiments, it was demonstrated that KLVFF binds stereo specifically to the homologous sequence in A.beta. (i.e. . A.beta.-16-20). By screening combinatorial pentapeptide libraries exclusively composed of D-amino acids (lowercase) with labelled KLVFF, several ligands with a motif containing phenylalanine (f) in the second and leucine (l) in the third position were identified (e.g. lflrr). By using a short peptide in the screening, known to bind to a region in A.beta. critical for its polymerization (i.e. KLVFF), the risk of identifying D-pentapeptides that interact with nonrelevant regions in A.beta. (N- or C-terminal to A.beta.-16-20) was eliminated. Like KLVFF, the D-amino acid ligands were found not only to bind to A.beta. but also to inhibit amyloid fibril formation. Since peptides built up of D-amino acids are resistant to proteolytic degradation, these ligands way be beneficial for inhibition of amyloidogenesis in vivo. The results further indicate that KLVFF will be useful in the identification of small organic molecules (e.g. by screening of substance libraries) with the ability to bind to A.beta. in this relevant region and inhibit amyloid fibril formation (candidate drugs for the treatment of Alzheimer disease and other related amyloidoses).

13. Document ID: US 20020094335 A1

L4: Entry 13 of 21 File: PGPB Jul 18, 2002

DOCUMENT-IDENTIFIER: US 20020094335 A1
TITLE: Vaccine for the prevention and treatment of alzheimer's and amyloid related diseases

Detail Description Paragraph:
[0081] Specifically, the A.beta.(16-21) site is known to play an important role in initiating the harmful process of A.beta. peptide amyloidogenesis. It is also known

that when these peptides are made from D-amino acids, they retain their ability to interact with the natural all-L-homologous sequence, thereby preventing amyloidogenesis. Other amyloid proteins which may be used in the present invention include, without limitation, the beta sheet region of IAPP (24-29, all-D), .beta.2-microglobulin, amyloid A protein, and prion-related proteins.

14. Document ID: US 6831066 B2

L4: Entry 14 of 21 File: USPT Dec 14, 2004

DOCUMENT-IDENTIFIER: US 6831066 B2
TITLE: Modulators of .beta.-amyloid peptide aggregation

Brief Summary Text (9):
This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural .beta.-APs. The compounds are modified in a manner which allows for increased biostability and prolonged elevated plasma levels. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is an inverso isomer of an L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP, or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO:4). In preferred embodiments, a phenylalanine in the compounds of the invention is. substituted with a phenylalanine analogue which is more stable and less prone to, for example, oxidative metabolism, or allows for increased brain levels of the compound.

Brief Summary Text (10):
In yet another embodiment, a modulator compound of the invention includes a .beta.-amyloid peptide comprised of D-amino acids, L-amino acids or both, an inverso isomer of a .beta.-amyloid peptide, or a retro-inverso isomer of a .beta.-amyloid peptide which is attached to a hydrazine moiety, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides.

Detailed Description Text (11):
As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect and/or may improve the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid

substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (e.g., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found within a parent peptide but in which all L-amino acids have been substituted with all D-amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detailed Description Text (12):
As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D-Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman et al "Perspectives in Peptide Chemistry" pp. 283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detailed Description Text (15):
In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In preferred embodiments, a phenylalanine in the compounds of the invention is substituted with a phenylalanine analogue which is more stable and less prone to, for example, oxidative metabolism.

Detailed Description Text (17):
In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In preferred embodiments, the phenylalanines in the compounds of the invention are substituted with phenylalanine analogues which are more stable and less prone to, for example, oxidative metabolism.

Detailed Description Text (19):
In yet another embodiment, a modulator compound of the invention includes a .beta.-amyloid peptide comprised entirely or partially of D-amino acids, an inverso isomer of a .beta.-amyloid peptide, or a retro-inverso isomer of a .beta.-amyloid peptide which is attached to a hydrazine moiety, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the modulator compound of the invention is comprised of 1-20 D-amino acids, more preferably 1-10 D-amino acids, even more preferably 1-5 D-amino acids, and most preferably 2-4 D-amino acids which are attached to a hydrazine moiety.

15. Document ID: US 6689752 B2

L4: Entry 15 of 21 File: USPT Feb 10, 2004

DOCUMENT-IDENTIFIER: US 6689752 B2
TITLE: Modulators of .beta.-amyloid peptide aggregation comprising D-amino acids

Brief Summary Text (9):
This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural .beta.-APs. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO: 3).

Detailed Description Text (11):
As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (e.g., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found within a parent peptide but in which all L-amino acids have been substituted with all D-amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detailed Description Text (12):
As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D-Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman et al "Perspectives in Peptide Chemistry" pp. 283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detailed Description Text (15):
In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid

peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the .beta.-amyloid peptide of the modulator is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the .beta.-amyloid peptide of the modulator is carboxy-terminally modified, for example the modulator can comprise a peptide amide, a peptide alkyl or aryl amide (e.g., a peptide phenethylamide) or a peptide alcohol. Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The .beta.-amyloid peptide of the modulator may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, .beta.-amyloid peptide of the modulator may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (16):
In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the retro-inverso isomer is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the retro-inverso isomer is carboxy-terminally modified, for example with an amide group, an alkyl or aryl amide group (e.g., phenethylamide) or a hydroxy group (i.e., the reduction product of a peptide acid, resulting in a peptide alcohol). Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The retro-inverso isomer may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, the retro-inverso isomer may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (141):
In this example, the necessity for an N-terminal modifying group on the D-amino acid-based modulator compounds was evaluated. Peptides comprised entirely of D-amino acids and having a free amino terminus were prepared and tested for their ability to inhibit aggregation of natural .beta.-amyloid peptide using aggregations assays as described in Example 2. Abbreviations used in this example and presentation of the data are the same as described in Example 3. The results are shown below in Table VI. Compounds exhibiting a change in lag time (.DELTA.Lag) of 1.3 or greater are highlighted in bold.

Detailed Description Text (142):
The results shown in Table VI demonstrate that modulators comprising all D-amino acids and having a free amino terminus are effective at inhibiting aggregation of natural .beta.-amyloid peptides (i.e., an N-terminal modifying group is not required for the D-amino acid-containing modulators to effectively inhibit aggregation of natural .beta.-amyloid peptides). A particularly preferred D-amino acid modulator compound having a free amino-terminus is PPI-579, the retro-inverso isomer of A.beta..sub.17-21 (A.sub.21.fwdarw.F) with a C-terminal amide.

16. Document ID: US 6610658 B1

L4: Entry 16 of 21 File: USPT Aug 26, 2003

DOCUMENT-IDENTIFIER: US 6610658 B1
**** See image for Certificate of Correction ****
TITLE: Modulators of .mu.-amyloid peptide aggregation

Brief Summary Text (9):
This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural .beta.-APs. The compounds are modified in a manner which allows for increased biostability and prolonged elevated plasma levels. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is an inverso isomer of an L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP, or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO:4). In preferred embodiments, a phenylalanine in the compounds of the invention is substituted with a phenylalanine analogue which is more stable and less prone to, for example, oxidative metabolism, or allows for increased brain levels of the compound.

Brief Summary Text (10):
In yet another embodiment, a modulator compound of the invention includes a .beta.-amyloid peptide comprised of D-amino acids, L-amino acids or both, an inverso isomer of a .beta.-amyloid peptide, or a retro-inverso isomer of a .beta.-amyloid peptide which is attached to a hydrazine moiety, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides.

Detailed Description Text (11):
As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect and/or may improve the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (eg., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found

within a parent peptide but in which all L-amino acids have been substituted with all D-amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detailed Description Text (12):
As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D-Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman et al. "Perspectives in Peptide Chemistry" pp. 283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detailed Description Text (15):
In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In preferred embodiments, a phenylalanine in the compounds of the invention is substituted with a phenylalanine analogue which is more stable and less prone to, for example, oxidative metabolism.

Detailed Description Text (17):
In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In preferred embodiments, the phenylalanines in the compounds of the invention are substituted with phenylalanine analogues which are more stable and less prone to, for example, oxidative metabolism.

Detailed Description Text (19):
In yet another embodiment, a modulator compound of the invention includes a .beta.-amyloid peptide comprised entirely or partially of D-amino acids, an inverso isomer of a .beta.-amyloid peptide, or a retro-inverso isomer of a .beta.-amyloid peptide which is attached to a hydrazine moiety, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the modulator compound of the invention is comprised of 1-20 D-amino acids, more preferably 1-10 D-amino acids, even more preferably 1-5 D-amino acids, and most preferably 2-4 D-amino acids which are attached to a hydrazine moiety.

17. Document ID: US 6331440 B1

L4: Entry 17 of 21 File: USPT Dec 18, 2001

DOCUMENT-IDENTIFIER: US 6331440 B1
TITLE: Peptide binding the KLVFF-sequence of amyloid-.beta.

Detailed Description Text (26):
In an additional series of experiments, it was demonstrated that KLVFF binds stereo specifically to the homologous sequence in A.beta. (i.e. A.beta.-16-20). By screening combinatorial pentapeptide libraries exclusively composed of D-amino acids (lowercase) with labelled KLVFF, several ligands with a motif containing phenylalanine (f) in the second and leucine (l) in the third position were identified (e.g. lflrr). By using a short peptide in the screening, known to bind to a region in A.beta. critical for its polymerization (i.e. KLVFF), the risk of identifying D-pentapeptides that interact with nonrelevant regions in A.beta. (N- or C-terminal to A.beta.-16-20) was eliminated. Like KLVFF, the D-amino acid ligands were found not only to bind to A.beta. but also to inhibit amyloid fibril formation. Since peptides built up of D-amino acids are resistant to proteolytic degradation, these ligands may be beneficial for inhibition of amyloidogenesis in vivo. The results further indicate that KLVFF will be useful in the identification of small organic molecules (e.g. by screening of substance libraries) with the ability to bind to A.beta. in this relevant region and inhibit amyloid fibril formation (candidate drugs for the treatment of Alzheimer disease and other related amyloidoses).

☐ 18. Document ID: US 6303567 B1

L4: Entry 18 of 21 File: USPT Oct 16, 2001

DOCUMENT-IDENTIFIER: US 6303567 B1
**** See image for Certificate of Correction ****
TITLE: Modulators of .beta.-amyloid peptide aggregation comprising D-amino acids

Brief Summary Text (9):
This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural .beta.-APs. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO: 3). Particularly preferred D-amino acid peptidic structures of the modulator comprise the retro-inverso isomers A.beta..sub.17-21, namely D-Ala-D-Phe-D-Phe-D-Val-D-Leu (SEQ ID NO: 4), or substituted versions thereof, such as D-Ala-D-Phe-D-Phe-D-Leu-D-Leu (SEQ ID NO: 5),

D-Leu-D-Phe-D-Phe-D-Val-D-Leu (SEQ ID NO: 6), D-Phe-D-Phe-D-Phe-D-Val-D-Leu (SEQ ID NO: 7), D-Phe-D-Phe-D-Phe-D-Leu-D-Val (SEQ ID NO: 24), D-Phe-D-Phe-D-Phe-D-Phe-D-Leu (SEQ ID NO: 25) and D-Ala-D-Phe-D-Phe-D-Phe-D-Leu (SEQ ID NO: 26).

Detailed Description Text (10):
As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (e.g., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found within a parent peptide but in which all L-amino acids have been substituted with all D-amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detailed Description Text (11):
As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman el al. "Perspectives in Peptide Chemistry" pp. 283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detailed Description Text (14):
In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the .beta.-amyloid peptide of the modulator is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the .beta.-amyloid peptide of the modulator is carboxy-terminally modified, for example the modulator can comprise a peptide amide, a peptide alkyl or aryl amide (e.g., a peptide phenethylamide) or a peptide alcohol. Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The .beta.-amyloid peptide of the modulator may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, .beta.-amyloid peptide of the modulator may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (15):
In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the

neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the retro-inverso isomer is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the retro-inverso isomer is carboxy-terminally modified, for example with an amide group, an alkyl or aryl amide group (e.g., phenethylamide) or a hydroxy group (i.e., the reduction product of a peptide acid, resulting in a peptide alcohol). Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The retro-inverso isomer may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, the retro-inverso isomer may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (152):
In another embodiment, the invention provides a peptide compound selected from the group consisting of A.beta..sub.14-21 (SEQ ID NO: 28), A.beta..sub.14-20 (SEQ ID NO: 29), A.beta..sub.15-21 (SEQ ID NO: 30), A.beta..sub.15-20 (SEQ ID NO: 31), A.beta..sub.16-21 (SEQ ID NO: 32), A.beta..sub.16-20 (SEQ ID NO: 46), A.beta..sub.17-21 (SEQ ID NO: 3) and A.beta..sub.17-20 (SEQ ID NO: 8), wherein at least one L-amino acid of the peptide compound is substituted with a D-amino acid. In another embodiment, this peptide compound is modified at its amino-terminus, its carboxy-terminus or both its amino- and carboxy-terminal with at least one modifying group that confers on the compound the ability to modulate the aggregation or inhibit the neurotoxicity of natural .beta.-amyloid peptides when the compound is contacted with the natural .beta.-amyloid peptides or that alters a pharmacokinetic property of the compound. In another embodiment of the peptide compound, all L-amino acids of the peptide compound are substituted with D-amino acids. In another embodiment of this latter compound, the compound is modified at its amino-terminus, its carboxy-terminus or both its amino- and carboxy-terminal with at least one modifying group that confers on the compound the ability to modulate the aggregation or inhibit the neurotoxicity of natural .beta.-amyloid peptides when the compound is contacted with the natural .beta.-amyloid peptides or that alters a pharmacokinetic property of the compound.

Detailed Description Text (216):
In this example, the necessity for an N-terminal modifying group on the D-amino acid-based modulator compounds was evaluated. Peptides comprised entirely of D-amino acids and having a free amino terminus were prepared and tested for their ability to inhibit aggregation of natural .beta.-amyloid peptide using aggregations assays as described in Example 2. Abbreviations used in this example and presentation of the data are the same as described in Example 3. The results are shown below in Table VI. Compounds exhibiting a change in lag time (.DELTA.Lag) of 1.3 or greater are highlighted in bold.

Detailed Description Text (217):
The results shown in Table VI demonstrate that modulators comprising all D-amino acids and having a free amino terminus are effective at inhibiting aggregation of natural .beta.-amyloid peptides (i.e., an N-terminal modifying group is not required for the D-amino acid-containing modulators to effectively inhibit aggregation of natural .beta.-amyloid peptides). A particularly preferred D-amino acid modulator compound having a free amino-terminus is PPI-579, the retro-inverso isomer of A.beta..sub.17-21 (A.sub.21.fwdarw.F) with a C-terminal amide.

CLAIMS:

1. A .beta.-amyloid modulator compound comprising a peptide comprised entirely of D-amino acids and having at least three amino acid residues independently selected from the group consisting of a D-leucine structure, a D-phenylalanine structure, a D-tyrosine structure, a D-iodotyrosine structure and a D-alanine structure, the peptide consisting of 3-5 amino acid residues, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides.

☐ 19. Document ID: US 6277826 B1

L4: Entry 19 of 21 File: USPT Aug 21, 2001

DOCUMENT-IDENTIFIER: US 6277826 B1
TITLE: Modulators of .beta.-amyloid peptide aggregation comprising D-amino acids

Brief Summary Text (9):
This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural (.beta.-APs. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO:3).

Detailed Description Text (11):
As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (e.g., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found within a parent peptide but in which all L-amino acids have been substituted with all D-amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detailed Description Text (12):
As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as

used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D-Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman et al. "Perspectives in Peptide Chemistry" pp.283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detailed Description Text (15):
In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the .beta.-amyloid peptide of the modulator is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the .beta.-amyloid peptide of the modulator is carboxy-terminally modified, for example the modulator can comprise a peptide amide, a peptide alkyl or aryl amide (e.g., a peptide phenethylamide) or a peptide alcohol. Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The .beta.-amyloid peptide of the modulator may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, .beta.-amyloid peptide of the modulator may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (16):
In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the retro-inverso isomer is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the retro-inverso isomer is carboxy-terminally modified, for example with an amide group, an alkyl or aryl amide group (e.g., phenethylamide) or a hydroxy group (i.e., the reduction product of a peptide acid, resulting in a peptide alcohol). Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The retro-inverso isomer may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, the retro-inverso isomer may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (148):
In this example, the necessity for an N-terminal modifying group on the D-amino acid-based modulator compounds was evaluated. Peptides comprised entirely of D-amino acids and having a free amino terminus were prepared and tested for their ability to inhibit aggregation of natural .beta.-amyloid peptide using aggregations

assays as described in Example 2. Abbreviations used in this example and presentation of the data are the same as described in Example 3. The results are shown below in Table VI. Compounds exhibiting a change in lag time (.DELTA.Lag) of 1.3 or greater are highlighted in bold.

Detailed Description Text (149):
The results shown in Table VI demonstrate that modulators comprising all D-amino acids and having a free amino terminus are effective at inhibiting aggregation of natural .beta.-amyloid peptides (i.e., an N-terminal modifying group is not required for the D-amino acid-containing modulators to effectively inhibit aggregation of natural .beta.-amyloid peptides). A particularly preferred D-amino acid modulator compound having a free amino-terminus is PPI-579, the retro-inverso isomer of A.beta..sub.17-21 (A.sub.21.fwdarw.F) with a C-terminal amide.

☐ 20. Document ID: US 6172043 B1

L4: Entry 20 of 21 File: USPT Jan 9, 2001

DOCUMENT-IDENTIFIER: US 6172043 B1
**** See image for Certificate of Correction ****
TITLE: Treatments for neurotoxicity in Alzheimer's disease caused by .beta. amyloid peptides

Brief Summary Text (12):
According to another aspect of the invention, a composition is provided. The composition includes a decoy peptide which binds to a neurotoxic .beta.-amyloid peptide and reduces the ability of the neurotoxic .beta.-amyloid peptide to form aggregates which increase calcium influx into neuronal cells, preferably NT2-N cells differentiated with retinoic acid. Preferably the decoy peptide is non-hydrolyzable, particularly a decoy peptide selected from the group consisting of peptides comprising D-amino acids, peptides comprising a --psi[CH.sub.2 NH]-- reduced amide peptide bond, peptides comprising a --psi[COCH.sub.2]-- ketomethylene peptide bond, peptides comprising a --psi[CH(CN)NH]-- (cyanomethylene)amino peptide bond, peptides comprising a --psi[CH.sub.2 CH(OH)]-- hydroxyethylene peptide bond, peptides comprising a --psi[CH.sub.2 O]-- peptide bond, and peptides comprising a --psi[CH.sub.2 S]-- thiomethylene peptide bond. In other embodiments, the decoy peptide binds to a neurotoxic .beta.-amyloid peptide is selected from the group consisting of .beta.AP.sub.1-42 and .beta.AP.sub.25-35. Preferably, the decoy peptide has .beta.-sheet forming potential, and is between 4 and 20 amino acids in length. More preferably, the decoy peptide is between 5 and 10 amino acids in length. Optionally, the decoy peptide can be a cyclized peptide.

Detailed Description Text (19):
Decoy peptide candidates can be selected initially, for example, by screening libraries of peptides for those peptides which have the ability to disrupt .beta.-amyloid peptide aggregate formation. Preferably, the library includes peptides which have .beta.-sheet forming potential. .beta.-sheet forming potential of peptides can be predicted from the amino acid sequence of the peptide by a known algorithm, such as the Chou-Fasman algorithm, which preferably applies equally to peptides containing D-amino acids. Peptide libraries may be structured so that peptides having .beta.-sheet forming potential are preferentially included.

Detailed Description Text (24):

Preferably, decoy peptidets are non-hydrolyzable. To provide such peptides, one may select decoy peptides from a library non-hydrolyzable peptides, such as peptides containing one or more D-amino acids or peptides containing one or more non-hydrolyzable peptide bonds linking amino acids. Alternatively, one can select peptides which are optimal for disrupting .beta.-amyloid peptide aggregation and then modify such peptides as necessary to reduce the potential for hydrolysis by proteases. For example, to determine the susceptibility to proteolytic cleavage, peptides may be labeled and incubated with cell extracts or purified proteases and then isolated to determine which peptide bonds are susceptible to proteolysis, e.g., by sequencing peptides and proteolytic fragments. Alternatively, potentially susceptible peptide bonds can be identified by comparing the amino acid sequence of a decoy peptide with the known cleavage site specificity of a panel of proteases. Based on the results of such assays, individual peptide bonds which are susceptible to proteolysis can be replaced with non-hydrolyzable peptide bonds by in vitro synthesis of the peptide.

☐ 21. Document ID: US 5985242 A

L4: Entry 21 of 21 File: USPT Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5985242 A
TITLE: Modulators of .beta.-amyloid peptide aggregation comprising D-amino acids

Brief Summary Text (9):
This invention pertains to compounds, and pharmaceutical compositions thereof, that can bind to natural .beta. amyloid peptides (.beta.-AP), modulate the aggregation of natural .beta.-AP and/or inhibit the neurotoxicity of natural .beta.-APs. The .beta.-amyloid modulator compounds of the invention comprise a peptidic structure, preferably based on .beta.-amyloid peptide, that is composed entirely of D-amino acids. In various embodiments, the peptidic structure of the modulator compound comprises a D-amino acid sequence corresponding to a L-amino acid sequence found within natural .beta.-AP, a D-amino acid sequence which is a retro-inverso isomer of an L-amino acid sequence found within natural .beta.-AP or a D-amino acid sequence that is a scrambled or substituted version of an L-amino acid sequence found within natural .beta.-AP. Preferably, the D-amino acid peptidic structure of the modulator is designed based upon a subregion of natural .beta.-AP at positions 17-21 (A.beta..sub.17-20 and A.beta..sub.17-21, respectively), which has the amino acid sequences Leu-Val-Phe-Phe-Ala (SEQ ID NO: 3).

Detailed Description Text (11):
As used herein, the term ".beta. amyloid peptide comprised entirely of D-amino acids", as used in a modulator of the invention, is intended to encompass peptides having an amino acid sequence identical to that of the natural sequence in APP, as well as peptides having acceptable amino acid substitutions from the natural sequence, but which is composed of D-amino acids rather than the natural L-amino acids present in natural .beta.-AP. Acceptable amino acid substitutions are those that do not affect the ability of the D-amino acid-containing peptide to alter natural .beta.-AP aggregation. Moreover, particular amino acid substitutions may further contribute to the ability of the peptide to alter natural .beta.-AP aggregation and/or may confer additional beneficial properties on the peptide (e.g., increased solubility, reduced association with other amyloid proteins, etc.). A peptide having an identical amino acid sequence to that found within a parent peptide but in which all L-amino acids have been substituted with all D-

amino acids is also referred to as an "inverso" compounds. For example, if a parent peptide is Thr-Ala-Tyr, the inverso form is D-Thr-D-Ala-D-Tyr.

Detailed Description Text (12):
As used herein, the term "retro-inverso isomer of a .beta. amyloid peptide", as used in a modulator of the invention, is intended to encompass peptides in which the sequence of the amino acids is reversed as compared to the sequence in natural .beta.-AP and all L-amino acids are replaced with D-amino acids. For example, if a parent peptide is Thr-Ala-Tyr, the retro-inverso form is D-Tyr-D-Ala-D-Thr. Compared to the parent peptide, a retro-inverso peptide has a reversed backbone while retaining substantially the original spatial conformation of the side chains, resulting in a retro-inverso isomer with a topology that closely resembles the parent peptide. See Goodman et al. "Perspectives in Peptide Chemistry" pp. 283-294 (1981). See also U.S. Pat. No. 4,522,752 by Sisto for further description of "retro-inverso" peptides.

Detailed Description Text (15):
In one embodiment, a modulator compound of the invention comprises a .beta.-amyloid peptide, the .beta.-amyloid peptide being comprised entirely of D-amino acids, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the .beta.-amyloid peptide of the modulator is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the .beta.-amyloid peptide of the modulator is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the .beta.-amyloid peptide of the modulator is carboxy-terminally modified, for example the modulator can comprise a peptide amide, a peptide alkyl or aryl amide (e.g., a peptide phenethylamide) or a peptide alcohol. Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The .beta.-amyloid peptide of the modulator may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, .beta.-amyloid peptide of the modulator may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (16):
In another embodiment, a modulator compound of the invention comprises a retro-inverso isomer of a .beta.-amyloid peptide, wherein the compound binds to natural .beta.-amyloid peptides or modulates the aggregation or inhibits the neurotoxicity of natural .beta.-amyloid peptides when contacted with the natural .beta.-amyloid peptides. Preferably, the retro-inverso isomer of the .beta.-amyloid peptide is comprised of 3-20 D-amino acids, more preferably 3-10 D-amino acids, and even more preferably 3-5 D-amino acids. In one embodiment, the retro-inverso isomer is amino-terminally modified, for example with a modifying group comprising a cyclic, heterocyclic, polycyclic or branched alkyl group. Examples of suitable N-terminal modifying groups are described further in subsection II below. In another embodiment, the retro-inverso isomer is carboxy-terminally modified, for example with an amide group, an alkyl or aryl amide group (e.g., phenethylamide) or a hydroxy group (i.e., the reduction product of a peptide acid, resulting in a peptide alcohol). Examples of suitable C-terminal modifying groups are described further in subsections II and III below. The retro-inverso isomer may be modified to enhance the ability of the modulator to alter .beta.-AP aggregation or neurotoxicity. Additionally or alternatively, the retro-inverso isomer may be modified to alter a pharmacokinetic property of the modulator and/or to label the modulator with a detectable substance (described further in subsection III below).

Detailed Description Text (145):
In this example, the necessity for an N-terminal modifying group on the D-amino acid-based modulator compounds was evaluated. Peptides comprised entirely of D-amino acids and having a free amino terminus were prepared and tested for their ability to inhibit aggregation of natural .beta.-amyloid peptide using aggregations assays as described in Example 2. Abbreviations used in this example and presentation of the data are the same as described in Example 3. The results are shown below in Table VI. Compounds exhibiting a change in lag time (.DELTA.Lag) of 1.3 or greater are highlighted in bold.

Detailed Description Text (146):
The results shown in Table VI demonstrate that modulators comprising all D-amino acids and having a free amino terminus are effective at inhibiting aggregation of natural .beta.-amyloid peptides (i.e., an N-terminal modifying group is not required for the D-amino acid-containing modulators to effectively inhibit aggregation of natural .beta.-amyloid peptides). A particularly preferred D-amino acid modulator compound having a free amino-terminus is PPI-579, the retro-inverso isomer of A.beta..sub.17-21 (A.sub.21 .fwdarw.F) with a C-terminal amide.

Term	Documents
AMYLOID	6874
AMYLOIDS	196
D-AMINO	6779
D-AMINOES	0
D-AMINOS	0
D-AMINOE	0
$PEPTIDE?	0
CARBAPEPTIDES	1
NONADECAPEPTIDES	1
NONADECAPEPTIDE]	3
TETRADECAPEPTIDES	16
(AMYLOID SAME $PEPTIDE? SAME (D-FORM? OR D-AMINO ACID? OR D4ISOMER?)).PGPB,USPT,USOC.	21

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